

AWARD NUMBER: W81XWH-11-C-0033

TITLE: Phase 2 Clinical Trials: D-Methionine to Reduce Noise-induced Hearing Loss

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REPORT DATE: July 2016

TYPE OF REPORT: Final

PREPARED FOR: U.S. Army Medical Research and Materiel Command
Fort Detrick, Maryland 21702-5012

DISTRIBUTION
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REPORT DOCUMENTATION PAGE		Form Approved OMB No. 0704-0188
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1. REPORT DATE July 2016	2. REPORT TYPE Final	3. DATES COVERED 1 March 2011 – 30 April 2016
4. TITLE AND SUBTITLE Phase 2 Clinical Trials: D-Methionine to Reduce Noise-Induced Hearing Loss		5a. CONTRACT NUMBER
		5b. GRANT NUMBER W81XWH-11-C-0033
		5c. PROGRAM ELEMENT NUMBER
		5d. PROJECT NUMBER
6. AUTHOR(S) Kathleen C.M. Campbell, PhD E-mail: kcampbell@siumed.edu E-Mail: kcampbell@siumed.edu		5e. TASK NUMBER
		5f. WORK UNIT NUMBER
7. PERFORMING ORGANIZATION NAME(S) AND ADDRESS(ES) Southern Illinois University School of Medicine Springfield, IL 62794-9629		8. PERFORMING ORGANIZATION REPORT NUMBER
9. SPONSORING / MONITORING AGENCY NAME(S) AND ADDRESS(ES) U.S. Army Medical Research and Materiel Command Fort Detrick, Maryland 21702-5012		10. SPONSOR/MONITOR'S ACRONYM(S)
		11. SPONSOR/MONITOR'S NUMBER(S)
12. DISTRIBUTION / AVAILABILITY STATEMENT Approved for Public Release		
13. SUPPLEMENTARY NOTES		
<p>14. ABSTRACT The purpose of this clinical trial was to determine if an oral D-methionine liquid suspension could prevent noise-induced hearing loss (NIHL) and tinnitus in our troops. This prospective study was a randomized, double-blind, placebo-controlled Phase 3 clinical trial. The goal was to develop a safe oral pharmacologic agent for noise exposures exceeding hearing protective device protective capabilities. The study population included Drill Sergeant (DS) instructor trainees at Fort Jackson, SC. At the end of this grant period, we enrolled 457 subjects, randomized 305 subjects, and 235 have completed all phases of the trial. Study drug was well tolerated with no reported serious adverse events. The IND, prepared and approved by FDA during this grant period, was transferred to a new biotech company, MetArmor, Inc. effective May 30, 2016. Enrollment continued with supplemental funding from MetArmor with an interim analysis in July 2016. The preliminary results of the interim analysis are included.</p>		
<p>15. SUBJECT TERMS D-methionine, Otoprotection, Noise-induced hearing loss (NIHL)</p>		

16. SECURITY CLASSIFICATION OF: Unclassified			17. LIMITATION OF ABSTRACT UU	18. NUMBER OF PAGES 24	19a. NAME OF RESPONSIBLE PERSON – USAMRMC
a. REPORT U	b. ABSTRACT U	c. THIS PAGE U			19b. TELEPHONE NUMBER

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INTRODUCTION:

This prospective study is a randomized, double-blind, placebo-controlled Phase 3 clinical trial of oral D-methionine to reduce NIHL and tinnitus. The study's goal is to develop a safe oral pharmacologic agent to augment physical hearing protectors for noise exposures that exceed the protective capabilities of ear plugs and/or muffs. The study population includes a cohort of Drill Sergeant School (DSS) Instructor candidates. The study's primary objective is to determine D-methionine's efficacy in preventing or reducing NIHL and tinnitus secondary to a minimum of 500 rounds of M-16 weapons training occurring over a 2-week period. The initial target enrollment goal was 600 DSS Instructor candidates with a final study cohort of 504 subjects. At the end of the grant period, we enrolled 457 subjects, randomized 305 subjects, and 252 have completed all phases of the study. An interim analysis to re-estimate the sample size for this trial is scheduled in July 2016. Enrollment continues with supplemental funding from our new biotech company, MetArmor, Inc.

STUDY GOALS: The purpose of this Phase 3 clinical trial is to determine if an oral, orange flavored suspension of D-methionine can prevent NIHL and tinnitus in our troops per the following specific aims:

Aim 1. To determine whether administering oral D-methionine can prevent permanent NIHL after weapons training. This aim will be addressed by comparing the results of D-methionine versus placebo administration starting 3 days prior to, during the 11-day period of weapons training, and 4 days after for a total of 18 days. Pure tone hearing thresholds will be assessed before and 15-16 days after completion of weapons training (i.e., 11-12 days after the last day of study drug/placebo administration).

Aim 2. To determine whether administering oral D-methionine can prevent tinnitus after weapons training. This aim will be addressed by comparing the results of D-methionine versus placebo administration starting 3 days prior to, during the 11-day period of weapons training, and 4 days after for a total of 18 days. Tinnitus questionnaires will be assessed before and 15-16 days after completion of weapons training (i.e., 11-12 days after the last day of study drug/placebo administration).

Aim 3. To monitor for any potential side effects of D-methionine. This aim will be accomplished by subject query on each day of drug administration with routing of any adverse event reports to study medical personnel, statisticians and to the Food and Drug Administration (FDA). Additional safety labs were added to the protocol beginning March 2016 upon FDA recommendation.

Funding and Approvals History: The Department of Defense Medical Research and Development Program (DMRDP) contract (10120007) was awarded starting April 1, 2010. An Investigational New Drug Application (IND) was submitted to the FDA and approved on August 13, 2012. Approval from Dwight D Eisenhower Army Medical Command (DDEAMC) Institutional Review Board (IRB) was obtained on June 13, 2013. Continuing Review (CR) approval for the clinical trial was obtained on May 12, 2016. Initial Human Research Protections Office (HRPO), USAMRMC was obtained on July 3, 2013 and CR Approval on July 9, 2015. There have been no lapses in regulatory reports or approvals (IRB, HRPO, FDA).

KEYWORDS:

D-methionine, noise, protection, hearing loss, antioxidant, free radicals, NIHL

ACCOMPLISHMENTS:

What were the major goals of the project?

SOW Task 1: To submit a complete Investigational New Drug (IND) Application to the FDA.

SOW Task 2: To submit a completed Institutional Review Board (IRB) application.

SOW Task 3: To complete the Hiring of Study Staff and finalize corporate contracts.

SOW Task 4: To complete study Site Visits.

SOW Task 5: To complete all necessary study documents.

SOW Task 6: To recruit subjects for first pilot data.

SOW Task 7: Send pilot data sent to Yale for data checking.

SOW Task 8: To continue enrollment and recruitment with new classes starting every 2-3 weeks

What was accomplished under these goals?

SOW Task 1: To submit a complete Investigational New Drug (IND) Application to the FDA.

Task completed. Our 15 volume IND application was prepared and submitted to FDA on May 23, 2012. We received FDA approval to proceed with our clinical trial on August 13, 2012.

SOW Task 2: To submit a completed Institutional Review Board (IRB) application.

Task completed. We received full DDEAMC IRB approval on June 13, 2013 to begin the study. We received our most recent DDEAMC continuing review (CR) approval on May 12, 2016. Initial HRPO approval was obtained on July 13, 2013. Our most recent HRPO CR approval was obtained on July 9, 2015. Our current HRPO CR approval is pending. There have been no lapses in approval during the conduct of this trial.

SOW Task 3: To complete the Hiring of Study Staff and finalize corporate contracts.

- a. Yale Occupational Environmental Medicine Program: Task completed. The original subcontract for Yale was signed and finalized. The Yale OEM Program serves as the Data Management Unit for this clinical trial. Dr. Carrie Redlich, MD, Martin Slade, MS, Meredith Stowe, PhD are responsible for data management and analysis.
- b. Fort Jackson: Task completed. On-site study coordinators, Elizabeth Bullock, R.N. and Shelley Laird, LPN, are in place and have been successfully recruiting and enrolling subjects. Audiologists from the Fort Jackson Army Hearing Program perform all protocol-related audiology assessments. On-site research monitors, as required by the DoD, have been appointed and approved by DDEAMC IRB. Currently, David Pavlakovich, PA-C, Moncrief Army Community Hospital (MACH), Department of Preventive Medicine, Fort Jackson, SC serves as the on-site research monitor. Site Principal Investigators have included: LTC Neil Page; MAJ William Callis, MD, COL William Bimson, DO; MAJ Christopher Wilson, MD; CPT William Grimes, MD. Pharmacy and laboratory support is also provided by MACH, Fort Jackson. Ombudsmen support is provided by the Fort Jackson Office of Volunteer Services.
- c. SIUSOM/ SIU Center for Clinical Research (CCR): Task completed. All study personnel have been recruited, trained and are currently working on different aspects of the project. Joseph Milbrandt, PhD serves as the Clinical Monitor for this clinical trial. Study monitors from SIU CCR have participated in all of the interim monitoring visits (5 to date). Jill Anderson, AUD, PhD participated as the initial off-site research coordinator until May, 2015. Daniel Fox, MPH, PhD joined the SIUSOM team as the off-site research coordinator beginning June 1, 2015. Sandra Puczynski, PhD has served as a regulatory consultant and advisor to the project.
- d. KP Pharmaceuticals: Task completed. KP Pharmaceutical Technology, Indianapolis, Indiana is the drug manufacturer for this clinical trial.
- e. FDA/Regulatory Advisor: Task completed. Judy Weissinger, PhD served as the FDA/Regulatory Advisor for this clinical trial from April 1, 2010 through October 30, 2015. Rick Lampe currently serves as the FDA/Regulatory Advisor for the clinical trial.
- f. Colleen Le Prell, PhD: Task completed. Dr. Le Prell's consulting contract was re-budgeted to reflect her significant decrease in active participation in the project. The funding for Dr. Le

Prell was re-budgeted to Dr. Weissinger for the work necessary to develop the IND and obtain FDA approval for this clinical trial as a Phase 3 study rather than the originally planned Phase 2 study.

SOW Task 4: To complete study Site Visits

- a. **August 7-8, 2012:** The study team, comprising Dr. Campbell, Dr. Milbrandt, and Dr. Puczynski (SIU CCR Director), traveled to the study site to meet key personnel, tour the facilities and gather data for logistics.
- b. **October 10-13, 2012:** Dr. Anderson, SIU study coordinator, traveled to the study site to upload study documents into the DDEAMC IRBNet since SIUSOM does not have access through Army Knowledge Online (AKO).
- c. **August 26-29, 2013:** Dr. Campbell, Dr. Puczynski, Dr. Anderson and Dr. Milbrandt traveled to the study site for the site initiation visit.
- d. **December 9-11, 2013:** Dr. Milbrandt traveled to the study site with one SIU CCR study monitor to complete the first on-site monitoring visit.
- e. **June 18-20, 2014:** Dr. Milbrandt traveled to the study site with two SIU CCR study monitors to complete the second on-site monitoring visit.
- f. **Sept 11-15, 2014:** Dr. Campbell traveled to the study site and met with the Fort Jackson and DSS leadership and study team members. She also gave a lecture at Fort Jackson attended by not only the DSS and study team members but also physicians from the Public Health command and other commands at Fort Jackson.
- g. **Sept 16, 2014:** AAR Research Project Audit completed by DDEAMC IRB. Only minor findings were reported with no to minimal impact on subject risk or safety.
- h. **Nov 19-20, 2014:** Dr. Milbrandt and two SIU CCR study monitors traveled to the study site to complete the third on-site monitoring visit.
- i. **June 4-6:** Dr. Campbell presented her research at the Joint Branches Drill SGT Academy Symposium and Open House at Fort Jackson.
- j. **June 8-9:** Dr. Campbell interviewed with the Wall Street Journal at Fort Jackson.
- k. **June 10-11, 2015:** Dr. Milbrandt and two SIU CCR study monitors traveled to the study site to complete the fourth on-site monitoring visit.
- l. **Dec 1-3, 2015:** Dr. Puczynski (SIU) and Martin Slade (Yale DMU) visited the Fort Jackson site to assess data collection, management, and reporting.
- m. **Dec 14-17, 2015:** Dr. Fox and two SIU CCR study monitors traveled to Fort Jackson to complete the fifth on-site monitoring visit.

SOW Task 5: To complete all necessary study documents.

Task completed. All study documents were initially approved by the DDEAMC IRB on June 13, 2013. We received DDEAMC continuing review approval on May 12, 2016. There have been no lapses in regulatory approvals (IRB, HRPO, FDA). There is a Manual of Operations for the trial.

SOW Task 6: To recruit subjects for first pilot data.

Task completed. The first of two groups of pilot subjects were recruited and enrolled on October 7, 2013 and October 10, 2013. The total number of participants completing the pilot study was nine.

SOW Task 7: Send pilot data sent to Yale for data checking

Task completed. All pilot data were successfully transferred to the Yale statisticians via REDCap, a data management system. Yale currently conducts quality checks on the data and provides enrollment, AE and other reports as requested for DoD, DDEAMC IRB, DSMC, FDA, etc.

SOW Task 8: To continue enrollment and recruitment with new classes starting every 2-3 weeks

Task ongoing. The original enrollment target was 600 subjects with an estimated attrition rate = 20%. An estimated 504 subjects are needed to complete all follow-up assessments (252 subjects per group) to detect significant differences for the primary outcome measures, unless the planned interim analysis (IA) indicates otherwise.

At the time of this report, 476 subjects have been consented to date and 305 (67%) have been randomized. Total randomized and treated to date = 271 with 34 currently on study. 254 subjects have completed the study to date; 12 more are scheduled to complete on June 27, 2016.

There are approximately 15 DSS classes each year with an average of 66 candidates per class (Range = 43-121). Approximately 18% of the candidates from each class have enrolled in the trial (Range = 4-29%). This percentage increased this year from 14% to 21%. The increase may be partially attributed to the subject stipends (\$50) for blood draws that were implemented in August 2015. There are six additional Drill Sergeant Academy (DSA) classes scheduled this year with the possibility that 1-2 additional classes might be added late fall 2016.

Screen failures and withdrawal rates remain fairly high at approximately 25%, respectively. Screen failures are primarily related to abnormal otologic exam or asymmetry. Withdrawals associated with an adverse event are minimal. Other reasons for withdrawal include compliance issues and failing DSA. Unexpected circumstances (flooding at Fort Jackson) led us to withdraw one entire class while on treatment (015-15; n=9) and, not recruit from class 016-15. Class 006-16 (n=4) had to be withdrawn because the PI had to be off-site.

Adverse event information is collected at each dosing and end of study. Additional safety assessments (blood and urine samples collected pre-, during and post-treatment) were recently added to the protocol per FDA recommendation. No serious adverse events have been reported to date.

We anticipate being able to enroll approximately 100 more subjects (~15 per class) by October 31, 2016. The interim analysis (IA) is scheduled in Q3 2016 to re-estimate the sample size necessary to complete the trial. With no interruptions, we project reaching a 2016 enrollment goal of 577 subjects (96% target). We may need to recruit into the first quarter of 2017 to reach 600 subjects, possibly longer if we still need 504 subjects for final statistical analysis.

What opportunities for training and professional development has the project provided?

Everyone involved in this clinical trial has learned valuable lessons about working with the DoD and planning, coordinating and successfully conducting a clinical trial on a military base. Our on-site research team was fully integrated into the Drill Sergeant School Command's introductory briefings and After Action meetings. The DSA provided office space and communicated regularly with our study team about anticipated and unanticipated changes in the DSA schedule. Study coordinators had to be very flexible so not to interfere with the DSA training schedule/requirements often driving to the weapons range before 5AM to ensure study subjects received study drug in accordance with the protocol.

How were the results disseminated to communities of interest?

Nothing to Report. We have no results to report at this time, but progress about the trial has been widely disseminated.

What do you plan to do during the next reporting period to accomplish the goals?

Nothing to Report.

IMPACT:

What was the impact on the development of the principal discipline(s) of the project?

For the military particularly, noise-induced hearing loss has high costs not only in financial but in human terms. Military efficacy frequently depends on hearing. For the dismounted soldier, Letowski 2003 described hearing as the most important sense for survival. Further, physical hearing protectors such as earmuffs and plugs have been found to provide insufficient hearing protection for many military exposures. Taggart in 2001 reported that 11% of marines had permanent hearing loss following recruit training even with all hearing conservation protocols in place. Hearing loss can render a soldier less able to detect and identify the enemy, less able to understand commands, particularly in background noise typical on the battlefield, and may permanently reduce quality of life. In some cases, hearing loss may preclude redeployment or result in less optimal job assignment.

From studies thus far it appears promising that we could administer an oral D-met formulation to humans that could prevent or reduce permanent noise induced hearing loss and possibly tinnitus. Further in animals we can first administer it starting several hours after the noise exposure and prevent permanent hearing loss which could be very useful for unexpected noise exposures. The current trial is still ongoing however the protective potential for our troops justifies the study's continuation.

The study is progressing significantly. We continue to recruit study subjects without reported serious adverse events (SAEs). Dr. Campbell works diligently to raise public attention regarding the crucial need for the availability of pharmacological otoprotective agent to treat/prevent noise-induced hearing loss.

Overall, we are very appreciative of the support and encouragement that we have received from the US Army Medical Research and Materiel Command, Fort Jackson Army Base Command, Drill Sergeant Academy Command, Moncrief Army Community Hospital, Yale University, University of Florida, KP Pharmaceuticals, SIUSOM clinical trials and grants offices, and our consultants who have been willing to patiently work with us on performing the extra work required for this collaboration to successfully move forward. This work contributed significantly to the establishment of a new biotech company, MetArmor, Inc. that will further develop D-methionine as an FDA-approved otoprotective agent. We are all fully committed to preventing noise-induced hearing loss and tinnitus in our troops.

What was the impact on other disciplines?

Nothing to Report.

What was the impact on technology transfer?

This research directly led to the initiation of a new start-up company, MetArmor, Inc. As recommended by DoD Operational Medicine, Dr. Campbell, in conjunction with her business partner Jennifer Seibert, started a new biotech company, MetArmor Inc., incorporated on August 28, 2015. Pursuant to an agreement between Southern Illinois University School of Medicine and MetArmor Inc., the ownership, with all rights, responsibilities and obligations, of the IND were transferred from SIU to MetArmor Inc. effective May 30, 2016. MetArmor, Inc. will further develop D-methionine for NIHL. Plans for a confirmatory clinical trial are underway as a final step towards eventual FDA new drug approval.

What was the impact on society beyond science and technology?

Noise-induced hearing loss is a common problem in society as a whole. The high incidence of noise induced hearing loss in our society can reduce the pool of applicants qualifying for military service. Although significant progress has been made in developing physical hearing protectors and in controlling work-related noise exposure, permanent noise-induced hearing loss (NIHL) still affects at least 10 million Americans (Lang 1994, Alberti et al 1998). Further, harmful levels of occupational noise exposure may affect close to 30 million Americans (Rabinowitz 2000). NIHL is also an international problem. According to the World Health Organization, exposure to excessive noise is the major avoidable cause of permanent hearing loss worldwide (Smith 1998). As well, recreational activity with firearms, amplified music, motorcycles, and power tools can expose millions of people to sound capable of producing permanent hearing loss (Metternich and Brusis 1999, Axelsson et al 1991, Rabinowitz 2000). Recently, studies have shown that even young children suffer from hearing loss after exposure to sudden noise emitted by toy pistols and firecrackers (Hellstrom 1992, Segal et al 2003).

This is the most advanced clinical trial for D-methionine protection from noise induced hearing loss conducted to date. In fact, we are further along than any other otoprotective agent in the world for this most common cause of hearing loss world-wide. Further our database is verified and certified with nearly 500 subjects enrolled to date and complete data collection on nearly 282 subjects.

CHANGES/PROBLEMS:

Changes in approach and reasons for change: Very few changes to the clinical protocol were made since the original grant submission. Some of the inclusion and exclusion criteria were modified (i.e., extending age range of participants to better represent the DSA population, including Reservists since they made up a significant portion of the DSA classes, permitting limited use of protein bars). We were also permitted to pay subjects for baseline blood draws in accordance with DoD requirements. This change had a modest impact on our recruitment and retention goals. This year, we added new blood and urine collections (pre-, during, and post-treatment) to obtain additional laboratory safety assessments (hematology, chemistry, liver function and homocysteine) per FDA recommendation. All protocol changes were approved by DDEAMC IRB prior to initiation.

Actual or anticipated problems or delays and actions or plans to resolve them: The majority of our IRB and HRPO amendments were caused by personnel changes at Fort Jackson. Site Principal Investigators, research monitors, study audiologists and DSA leaders were active-duty soldiers who were often reassigned with little notice. We worked very closely with Fort Jackson to anticipate these departures and acted quickly to ensure new personnel were committed, trained, oriented to the protocol, and remained compliant.

Recruitment of subjects was directly tied to the availability of DSA candidates. On average, there are 16 DSA classes per year and class sizes ranged from 43-121 candidates per class. DSA candidates are model soldiers who undergo a very rigorous training program with little free time. We anticipated higher recruitment rates, but the rigor of the weapons training program and pressure to successfully complete it were the soldiers' first priority. As mentioned previously, a modest stipend for blood draws improved our recruitment and retention rates somewhat.

Other delays or problems with recruitment included circumstances beyond our control, such as flooding in Columbia, SC that resulted in base closures, changes to the DSA schedule, etc. One entire class had to be withdrawn because the study drug was not available. Several soldiers had to be withdrawn because they failed the DSA training program and departed base on very short notice.

Changes that had a significant impact on expenditures: The most significant challenge we encountered was the time required to prepare the IND application and obtain the FDA and DDEAMC IRB approvals. The 15 volume IND application took about one year to prepare and the clinical trial

was approved to proceed by FDA on August 13, 2012. Subsequent DDEAMC IRB approval, which required the FDA IND approval, took approximately 10 more months despite only minor changes to the protocol required. CRADA execution was also delayed, but not within our control. We also underestimated the number of enrolled subjects who would fail the screening exams and/or withdraw from the study, however we had little prior data to rely on when making our initial estimates.

Significant changes in use or care of human subjects, vertebrate animals, biohazards, and/or select agents:

Nothing to report.

Significant changes in use or care of human subjects:

Nothing to report.

Significant changes in use or care of vertebrate animals:

Nothing to report.

Significant changes in use of biohazards and/or select agents

Nothing to report.

PRODUCTS:

Publications, conference papers, and presentations:

Invited External Presentations by Dr. Campbell that included this Phase 3 Clinical Trial (For Grant period only)

2011 Title: Otoprotective Agents for Noise and Drug Induced Hearing Loss. Audiology On-line Expert Seminar (Webinar) January 19, 2011

2011 Pharmacologic Otoprotective Agents: Current Status of Translational Research 2 hour lecture February 11, 2011 Sound Wave Symposium, San Diego, California

2011 Pharmacology and Audiology: What Every Audiologist Should Know Invited all day workshop, Pretoria, South Africa March 10, 2011

2011 Pharmacology and Audiology: What Every Audiologist Should Know Invited all day workshop, Durban, South Africa March 11, 2011

2011 Pharmacology and Audiology: What Every Audiologist Should Know Invited all day workshop, Cape Town, South Africa March 14, 2011

2011 Mechanisms of Drug and Noise Induced Hair Cell Death, Colleen LePrell and Kathleen Campbell. American Academy of Audiology: Audiology NOW Convention

Chicago Illinois, April 9, 2011 (Invited featured Session)

2011 Otoprotective Agents: On the Threshold of Clinical Use, Kathleen Campbell and Colleen LePrell American Academy of Audiology: Audiology NOW Convention

Chicago Illinois, April 9, 2011(Invited Featured Session)

2011Pharmacologic Protection for Noise Induced Hearing Loss. University College of London (MRC) Invited Seminar July 22, 2011 London, England

2011Pharmacologic Otoprotective Agents to Prevent Noise-Induced Hearing Loss (NIHL): When dietary concentration isn't enough: International Congress on the Biologic Effects of Noise. July 25, 2011 (Invited Featured Speaker) London, England

2011Tips for New Inventors: The Bench to Bedside Research Process. Kathleen C.M. Campbell 1 hour Phonak U.A mentoring 2.5 day workshop for AuD students across the country. Warrenville, IL August 3, 2011

2011New Frontiers in Otoprotective Agents. Kathleen C.M. Campbell 1 hour lecture Phonak U.A mentoring 2.5 day workshop for AuD students across the country. Warrenville, IL August 5, 2011

2011Faculty Panel: Mild Hearing Loss: Impact on Patients Kathleen C.M. Campbell 1 hour Phonak U.A mentoring 2.5 day workshop for AuD students across the country. Warrenville, IL August 7, 2010

2011 "Pharmacologic Prevention of Ototoxic and Noise Induced Hearing Loss" University College of London July 22, 2011

2011 "Pharmacologic Otoprotective Agents to Prevent Noise-Induced Hearing Loss (NIHL): When dietary concentration isn't enough" International Congress on Biologic Effects of Noise. London, England (invited featured lecture) July 25, 2011

2011 "Current Clinical Issues in Ototoxicity" Missouri Academy of Audiology, Fenton, Missouri (invited featured speaker) 1 hour September 8, 2011

2011 "Translational Research in Pharmacologic Otoprotective Agents: Bench to Bedside" Missouri Academy of Audiology, Fenton, Missouri 2 hours (invited featured speaker) September 8, 2011

2011Ototoxicity and Pharmacologic Otoprotective Agents: What every audiologist should know. California Academy of Audiology. Invited featured speaker 2 hour lecture San Diego, California Sept 23, 2011

2011"D-methionine as a Protective Agent" (invited Kathleen Campbell, SIUC Technology and Innovation Expo. October 28, 2011

2012"Pharmacologic Otoprotective Agents: On the threshold of clinical use" 1.5 hour lecture Invited Featured Speaker Illinois Academy of Audiology, Chicago Illinois, January 25, 2012

2012"D-methionine (D-met) Pre-Loading Prior to Noise Exposure Significantly Reduces Temporary and Permanent Noise-Induced Hearing Loss (NIHL) in Chinchillas Kathleen Campbell, Cathy Yu, Robert Meech, Daniel Fox, Steve Verhulst, Association for Research in Otolaryngology San Diego, California February 27, 2012

2012"Understanding Ototoxicity, Ototoxicity Monitoring, and New Otoprotective Agents for Otoxic and Noise-Induced Hearing Loss" Kaiser Permanente California Audiologists 6 hour lecture. May 22nd, 2012 Oakland, California

2012“Mechanisms of NIHL from impulse vs steady noise and effects of kurtosis” Invited Featured Speaker, American Industrial Hygiene Association national meeting. Indianapolis, Indiana June 19, 2012

2012“D-Methionine (D-Met) Clinical Trials for Noise-Induced Hearing Loss” Invited Lecture. Department of Defense Hearing Center for Excellence: HCE Pharmaceutical Interventions for Hearing Loss (PIHL) Advisory Board All-Hands Annual Meeting, Baltimore, MD August 23, 2012

2012“Logistics: Access, Line Leadership, CRADAs & Contracts, Oh My! Invited Panel, Richard Kopke, Tanisha Hammill, Kathy Cupp, Kathy Campbell Department of Defense Hearing Center for Excellence: HCE Pharmaceutical Interventions for Hearing Loss (PIHL) Advisory Board All-Hands Annual Meeting, Baltimore, MD August 24, 2012

2012“Study Measurements” Eric Bastings, Jonathan Kil, Kathleen Campbell, Kathy Cupp, Dawn Konrad-Martin, Lynne Marshall, Martin Slade, Rick Rogers, Sharon Kujawa Invited Panel Department of Defense Hearing Center for Excellence: HCE Pharmaceutical Interventions for Hearing Loss (PIHL) Advisory Board All-Hands Annual Meeting, Baltimore, MD August 24, 2012

2012“Understanding and Preventing Noise- and Drug-Induced Hearing Loss. Invited 90 minute presentation for the scientific lecture series for 3M Corporation. October 17, 2012 St. Paul, MN

2012“D-methionine as a Protective Agent: From Bench to Bedside Invited Lecture SIU Technology & Innovation Expo, October 19, 2012 Carbondale, IL (Named Inventor of the Year)

2012“Otoprotective Agents: On the Threshold of Clinical Use” 2 hour lecture, Texas Academy of Audiology, November 9 2012, San Antonio, TX

2013“Dose-Dependent D-Methionine Administration Significantly Reduces Permanent Impulse Noise-Induced Hearing Loss (NIHL) in Chinchillas. Association for Research In Otolaryngology , February 16, 2013 Baltimore, MD

2013“Clinical Trials” (invited lecture) National Hearing Conservation Association, St. Petersburg, FL February 21, 2013

2013“Pharmacologic Protection from Noise-Induced Hearing Loss in the U.S. Military National Hearing Conservation Association, St. Petersburg, FL February 21, 2013

2013Understanding Ototoxicity, Ototoxicity Monitoring, and New Otoprotective Agents for Ototoxic and Noise-Induced Hearing Loss. 6 hour workshop. Speech and Hearing Association of Alabama, Birmingham, AL March 9, 2013

2013“Reducing Cisplatin-induced Ototoxicity and Other Side Effects with D-methionine” Arizona Cancer Center, Tucson, AZ March 28, 2013 Visiting Professor

2013“Otoprotective Agents” Invited Featured Session, Audiology NOW, American Academy of Audiology, Anaheim, CA April 4, 2013

2013Audiology Unplugged, Invited session with AuD students with “Luminaries of Audiology” Audiology NOW, American Academy of Audiology, Anaheim, CA April 6, 2013

2013“Dose-dependent D-methionine Administration Significantly Reduces Permanent Impulse Noise-Induced Hearing Loss (NIHL) in Chinchillas” Poster session International Evoked

Audiometry Study Group biennial meeting, New Orleans, LA June 10, 2013

2013“Understanding Ototoxicity, Ototoxicity Monitoring, and New Otoprotective Agents for Ototoxic and Noise-Induced Hearing Loss” 5.5 hour workshop for Florida Academy of Audiology, Orlando FL August 9, 2013

2014“From Bench to Phase 3” Rebecca Ludwig, Jillyen Curry-Mathis, Kathleen Campbell, JDVAC Annual Conference, Las Vegas, NV March 11, 2014

2014“Ototoxicity and Otoprotective Agents” The Judy Gravel Lecture, The Children’s Hospital of Philadelphia, Philadelphia, PA Invited Featured Speaker, March 14, 2014

2014“ Clinical Issues in Ototoxicity: Agents and Patient Considerations, Ototoxicity Monitoring” Oregon Academy of Audiology, Wilsonville, Oregon April 12, 2014

2014“New Frontiers in Otoprotective Agents” Oregon Academy of Audiology, Wilsonville, Oregon April 12, 2014

2014“Phase 3 Clinical Trials to Prevent Noise-Induced Hearing Loss and Tinnitus in Soldiers” Midwest Auditory Research Conference and Midwest Auditory Neuroscience Symposium, July 18, 2014 Washington University, St. Louis, MO

2014“Guidance for Equipment, Personnel, Mechanical Process Overview, Audiologic Assessment Overview” Department of Defense, Hearing Center for Excellence, Pharmaceutical Interventions for Hearing Loss Working Group, All Hands Meeting Annapolis, MD August 7, 2014

2014“Outcomes and Lessons Learned from Clinical Trials” Department of Defense, Hearing Center for Excellence, Pharmaceutical Interventions for Hearing Loss Working Group, All Hands Meeting Annapolis, MD August 7, 2014

2014“The Adventure” Speaker as Scholar of Distinction 2014, Carbondale Convocation, Carbondale, IL August 15, 2014

2014 “From Bench to Phase 3 Clinical Trials:D-Methionine Pharmacological Agent to Prevent NIHL in Our Troops” Sept. 15, 2014 Fort Jackson, Columbia, SC

2014“Emerging Pharmacologic Treatments for Hearing Loss: Patient Considerations “Keynote Speaker All day seminar. JFK Medical Center, Edison, NJ October 24, 2014

2014 “The Role of Pharmaceutical Agents in Hearing Loss Management and Prevention”

Academy of Doctors of Audiology. Featured Speaker. Las Vegas, NV November 6, 2014

2014“Reducing Cisplatin Induced Ototoxicity and Other Side Effects with D-Methionine” St. Jude Children’s Research Hospital, Memphis, TN November 18, 2014

2015 “D-methionine (D-MET) administration, delayed up to 36 hours post-noise, significantly rescues from permanent steady state or impulse noise-induced hearing loss” Association for Research in Otolaryngology, Baltimore, MD. February 21, 2015

2015 “Mechanisms of Ototoxicity and Genomic Modulation” Peter Steyger and Kathleen Campbell Twenty First Annual Blood Brain Consortium Meeting. Skamania Lodge, Stevenson, WA March 19, 2015

2015 “Clinical Trial Designs for D-methionine Otoprotection” Kathleen Campbell Twenty First Annual Blood Brain Consortium Meeting. Skamania Lodge, Stevenson, WA March 20, 2015 “

2015 Otoprotection from Drug and Noise Induced Hearing Loss. Invited Featured 3 hour Session. Kathleen Campbell, Colleen LePrell American Academy of Audiology, San Antonio, TX April 2, 2015

2015 From Bench to Phase 3 Clinical Trials: D-Methionine Pharmacological Agent to Prevent NIHL in Our Troops. Invited Lecture for Drill Sergeant Instructor All Forces Open House, Ft. Jackson, SC June 5, 2015

2015 “Emerging Pharmacologic Treatments for Hearing Loss: Patient Considerations”Keynote Speaker All day seminar. Speech-Language-Pathology and Audiology of Canada, Calgary, Alberta, Canada June 19, 2015

2015 “New Frontiers in Pharmacologic Otoprotective Agents” Mensa Annual Gathering, Louisville, KY July 1, 2015

2015 “D-methionine (D-met) as an Otoprotective and Rescue Agent for Noise Induced Hearing Loss” MarcMans Conference, Omaha, NE July 23, 2015

2015 “D-methionine (D-met) Delayed Administration Post-Noise Cessation, Significantly Rescues Permanent Steady State or Impulse Noise Induced Auditory Threshold Shift in the Chinchilla” Military Health Research Symposium Ft. Lauderdale, FL August 20, 2015

2015 “The Role of Pharmaceutical Agents in Hearing Loss Management and Prevention” CUNY visiting professor, September 16, 2015

2015 “Phase 3 clinical trials to prevent noise induced hearing loss and tinnitus in our Soldiers” Ft, Rucker, Alabama, December 3, 2015

2016 “Bench to Bedside: Otoprotection and Patient Considerations for Ototoxic and Noise Induced Hearing Loss” All day invited workshop. National Hearing Conservation Association.(NHCA) San Diego, California February 18, 2016

2016 “Guidelines for Auditory Threshold Measurement for Significant Threshold Shift (STS) Department of Defense (DoD)” Hearing Center for Excellence (HCE) Pharmaceutical Intervention for Hearing Loss (PIHL) members: Kathleen Campbell; Colleen Le Prell; Michael Hoffer; Tanisha Hammill; Jonathan Kil Featured Podium Session Association for Research in San Diego, California February 21, 2016

2016 “D-methionine (D-met) Influences Endogenous Antioxidant Activity and Lipid Peroxidation by Dose- and Tissue-Specific Mechanisms” Poster session. Daniel Fox, Gregory Harpring, Robert Meech, Tim Hargrove, Steven Verhulst, Shelley Tischkau, Kathleen Campbell Association for Research in San Diego, California February 22, 2016

2016 “The Role of Pharmaceutical Agents in Hearing Loss Management and Prevention” Joint Defense Veterans AudiologyConvention (JDVAC) Kathleen Campbell, PhD Keynote Speaker, St. Louis, MO February 24, 2016

Journal publications:

Nothing to Report.

Books or other non-periodical, one-time publications:

Nothing to Report.

Other publications, conference papers, and presentations:

On August 22, 2015 this study was featured on the front page of the Wall Street Journal providing positive publicity not only for this clinical trial but for the DSS at Ft. Jackson. The article also educated the public about the problem of noise induced hearing loss and tinnitus in our troops and in the general public.

In January 2016 this clinical trial was featured in a 6-page article entitled “Armed and Exposed” published in the ASHA Leader, the official magazine of the American Speech Language and Hearing Association which goes out to its 186,000 members.

In February 2016, this work was included in a featured article in The Hearing Review.

Website(s) or other Internet site(s):

Nothing to Report.

Technologies or techniques:

Nothing to Report.

Inventions, patent applications, and/or licenses:

Nothing to Report.

Other Products:

Nothing to Report.

PARTICIPANTS AND OTHER COLLOBORATING ORGANIZATIONS:

What individuals have worked on the project? Please note that some lump sum funding was provided to the SIU Center for Clinical Research (CCR) for IND preparation, record keeping and study management. The months worked listed below only reflect those hours billed directly to the grant in addition to the CCR funding. Thus many of the staff working for the CCR worked hours and months in addition to those listed below for direct billing.

Name:	Kathleen Campbell, PhD
Project Role:	Primary Investigator
Researcher Identifier (e.g. ORCID ID):	N/A
Nearest person month worked:	13
Contribution to Project:	Designed and oversaw all aspects of the study, including personnel, data collection, standards, reporting, compliance, finance and budget, public relations and communications, audiology issues, Worked with all team members on their respective areas of responsibility and expertise.
Funding Support:	W81XWH-11-C-0033

Name:	Joseph Milbrandt, PhD
Project Role:	Clinical Monitor
Researcher Identifier (e.g. ORCID ID):	N/A
Nearest person month worked:	9
Contribution to Project:	Oversaw site monitoring and compliance activities. Arranged for the Center for Clinical Research Conference calls.
Funding Support:	W81XWH-11-C-0033

Name:	Leonard Rybak, MD, PhD
Project Role:	Independent Medical Monitor
Researcher Identifier (e.g. ORCID ID):	
Nearest person month worked:	3
Contribution to Project:	Worked with the site PI on AE reporting procedures and all subject safety issues.
Funding Support:	W81XWH-11-C-0033

Name:	Jill Anderson, AUD, PhD
Project Role:	Off-Site Research Coordinator
Researcher Identifier (e.g. ORCID ID):	N/A
Nearest person month worked:	1
Contribution to Project:	Developed and maintained RedCap data base entry for web sharing of data with Yale statisticians. Synthesized agendas for weekly conference calls. Took minutes and distributed them among team members. Helped prepare the FDA, IRB and HRPO documents for submission and kept the log of current documents.

Funding Support:	W81XWH-11-C-0033
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Name:	Daniel Fox, PhD, MPH
Project Role:	Off-Site Research Coordinator
Researcher Identifier (e.g. ORCID ID):	N/A
Nearest person month worked:	8
Contribution to Project:	Developed and maintained RedCap data base entry for web sharing of data with Yale statisticians. Synthesized agendas for weekly conference calls. Took minutes and distributed them among team members. Helped prepare the FDA, IRB and HRPO documents for submission and kept the log of current documents.
Funding Support:	W81XWH-11-C-0033

Name:	Sandra Puczynski, PhD
Project Role:	Project Consultant/Advisor
Researcher Identifier (e.g. ORCID ID):	N/A
Nearest person month worked:	1
Contribution to Project:	Regulatory consultant and advisor, Oversaw and generated all documents for FDA, IRB, HRPO, site compliance, human subject documents.
Funding Support:	W81XWH-11-C-0033

Name:	Carrie Redlich, MD, MPH
Project Role:	Environmental Health Physician. Statistician
Researcher Identifier (e.g. ORCID ID):	N/A
Nearest person month worked:	3
Contribution to Project:	Provided medical oversight for all data, data analysis and interpretation including hearing loss and tinnitus data, but also blood chemistry/laboratory work and adverse event classification and analysis.
Funding Support:	W81XWH-11-C-0033

Name:	Martin Slade, MS
Project Role:	Statistician
Researcher Identifier (e.g. ORCID ID):	N/A
Nearest person month worked:	6
Contribution to Project:	Designed and executed all statistical analysis in conjunction with Dr. Redlich

Funding Support:	W81XWH-11-C-0033
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Name:	Meredith Stowe, PhD
Project Role:	Data Manager
Researcher Identifier (e.g. ORCID ID):	N/A
Nearest person month worked:	
Contribution to Project:	Cross checked and verified all data entry with site coordinators. Prepared and managed database for statistical analysis.
Funding Support:	W81XWH-11-C-0033 through Geneva

Name:	Shelley Laird, LPN
Project Role:	Fort Jackson Study Coordinator
Researcher Identifier (e.g. ORCID ID):	N/A
Nearest person month worked:	32
Contribution to Project:	Provided the direct services for all aspects of study at Ft. Jackson. Drug shipments and coordination with pharmacy and laboratory. Collected blood samples and administered study drug/placebo. Data entry into Redcap system, Kept all site records in compliance with all guidances and regulations. Recruited and scheduled soldiers for study and coordinated all aspects of study with the base command. Worked under the supervision of Beth Bullock, RN.
Funding Support:	W81XWH-11-C-0033 through Geneva

Name:	D Bush, AUD, PhD
Project Role:	Back Up Audiologist
Researcher Identifier (e.g. ORCID ID):	N/A
Nearest person month worked:	1
Contribution to Project:	Provide PRN audiology support as needed (ie when base audiologists were not available for hearing testing,)
Funding Support:	W81XWH-11-C-0033

Name:	Elizabeth Bullock, RN, Research Nurse
Project Role:	Site Lead Research Coordinator

Researcher Identifier (e.g. ORCID ID):	N/A
Nearest person month worked:	32
Contribution to Project:	<p>Provided the direct services for all aspects of study at Ft. Jackson. Drug shipments and coordination with pharmacy and laboratory. Collected blood samples and administered study drug/placebo. Data entry into Redcap system, Kept all site records in compliance with all guidances and regulations.</p> <p>Recruited and scheduled soldiers for study and coordinated all aspects of study with the base command. Oversaw the work of Shelly Laird, LPN.</p>
Funding Support:	W81XWH-11-C-0033

Name:	Amber Stanton Fifer, PharmD
Project Role:	Monitor, PharmD advisor
Researcher Identifier (e.g. ORCID ID):	N/A
Nearest person month worked:	1
Contribution to Project:	<p>Served as site monitor including travel to Ft. Jackson, also provided advice on any issues related to pharmacy and pharmaceutical management.</p>
Funding Support:	W81XWH-11-C-0033

Name:	Julie Bullard, RN
Project Role:	Monitor
Researcher Identifier (e.g. ORCID ID):	N/A
Nearest person month worked:	1
Contribution to Project:	<p>Monitored data during the trial to ensure completion and compliance including travel to Ft. Jackson</p>
Funding Support:	W81XWH-11-C-0033

Name:	Judi Weissinger, PhD
Project Role:	FDA regulatory consultant
Researcher Identifier (e.g. ORCID ID):	N/A
Nearest person month worked:	2

Contribution to Project:	Prepared IND and all regulatory submissions in conjunction with the research team and the SIU Center for Clinical Research
Funding Support:	W81XWH-11-C-0033

Ft. Jackson staff who donated their time to this project: The exact hours of their generous time donation was not monitored. Please note that others listed on this project outside of Ft. Jackson donated countless additional hours of their time to the project such as Dr. Puczynski.

COL Neill Page, Site Principal Investigator; MAJ William Callis Site Principal Investigator; LTC William Bimson, Deputy Commander of Clinical Services, MACH, Site Principal Investigator; MAJ Christopher Wilson, Chief, Preventive Medicine MACH, Site Research Monitor and then site Principal Investigator; CPT Grimes, MD, IHMH, MACH Site Principal Investigator; COL Mark Higdon, Commander, Moncrief Army Community Hospital; COL Traci Crawford, Commander, Moncrief Army Community Hospital; CSM Michael McCoy, Commandant; US Army Drill SGT Academy; CSM Lamont Christian, Commandant; CSM Charles Gilmer, Commandant, US Army Drill SGT Academy; SM Edward Roderiques, Deputy Commandant, US Army Drill SGT Academy; SM Blaine Huston, Deputy Commandant, US Army Drill SGT Academy; MAJ Alfred Nader, Chief, Pathology, MACH; 1LT Joseph Newton, Assist. Chief, Pathology, MACH; CPT Calvina Glover, Chief, Laboratory, MACH; MAJ Tracy Morning, Chief, Pharmacy, MAJ Martin Ochoa, Chief, Pharmacy, MACH; CPT Gloria Lee, Pharm, Chief, Pharmacy MACH; CPT Jason Parsons, Chief, Pharmacy, MACH; MACH CPT MAJ Jillyen Curry-Mathis, Chief, Fort Jackson Hearing Program, Supervising Audiologist Rebecca Ludwig, Chief, Fort Jackson Hearing Program, Supervising Audiologist, Sub-Investigator CPT Virginia Bailey, Fort Jackson Hearing Program, Audiologist, Sub-Investigator CPT Jenny Davis, Chief, Fort Jackson Hearing Program, Supervising Audiologist, Sub-Investigator; CPT Eric Bunnell, Audiologist, Deputy Chief, Fort Jackson Hearing Program; MAJ Matthew Hanna, PA, Chief, Dept. of Soldier Care, MACH; Col Mark Packer, Otolaryngologist, Director of DoD Hearing Center for Excellence, Independent Medical Monitor Site Research Monitor; Mr. David Pavlakovich, Site Research Monitor; Raymond Wrywas, Audiologist Tech, SRC, MACH; Marie Johnson, RN, Dept of Preventive Medicine, MACH; Col Mark Packer, MD, Otolaryngologist, Director DoD Hearing Center for Excellence, Independent Medical Monitor, Ret. CMDR Royce Clifford, MD, Chair of DSMC through 2015

1SGT Heidi Miranda, MSG Leonard Taylor III, SDSLs Jason Endres, Keith Schmidt, Polly Schmidt, Eddie Vader, Melanie Coronado, Jason Bullock, Nicole Holmes, Christina Herring, Luis Figueroa, James Lawson, Reginald Smith, Christian Stokes, David Wardowski.

Ombudsmen Mr. Roosevelt Barnwell, Mr. Lin Wright, Ms. Marilyn Bailey, Mr. Jeffrey Bullock, Mr. Gregory Bullock, Ms. Linda Poole.

Has there been a change in the active other support of the PD/PI(s) or senior/key personnel since the last reporting period?

Nothing to Report.

What other organizations were involved as partners?

Organization Name: The Geneva Foundation
Location of Organization: Tacoma, WA

Partner's contribution to the project:

On-site study coordinator and back-up audiology support at Fort Jackson, SC.

Organization Name: MetArmor, Inc.
Location of Organization: P.O. Box 311
Glen Gardner, NJ 08826

Financial supplementation and license transfer.

Organization Name: KP Pharmaceutical Technologies
Location of Organization: Bloomington, IN

Formulation Supply and Shipping of GMP study drug and placebo.

SPECIAL REPORTING REQUIREMENTS:

Please see Quad Chart.

APPENDICES:

A: Intro to the Interim Analyses

B: D-met Efficacy Including Percent Reduction in Hearing Threshold Shift

C: Adverse Event (AE) Report

Appendix A: Introduction to the Interim Analysis

The following is a summary of the preliminary efficacy analysis on the n=260 patients included in the interim analysis.

1. Efficacy: Given that fewer than half the subjects required by the power analysis are included in this interim analysis, .05 efficacy could not be expected for any of the endpoints. In addition the incidence of hearing threshold shift in the control group was much lower than originally projected. Therefore the lack of statistical significance is not surprising. In general for the auditory threshold measures were better for the D-met treated than control groups. As can be seen from the attached table including the percentage reduction in incidence of hearing threshold shift for D-met versus placebo, the percent reduction in incidence is actually quite promising in that the reduction in incidence of early warning flag was over 40 percent. However for significant threshold shift the incidence even in the control group was less than 2 percent overall not allowing an analysis of reduction in incidence as even a single subject would influence the results. No protection from tinnitus was observed but the incidence of tinnitus in our clinical trial population was very low overall.
2. In analyzing the subject numbers needed based on the revised power analysis, MetArmor Inc decided that the additional development costs given the increased timeline and financial investment needed to determine efficacy were commercially prohibitive. Attached please find the statistical analysis prepared by Martin Slade MPH. Due to the lack of any clinically meaningful efficacy, MetArmor has decided to discontinue development of D-methionine.

3. Adverse Events: The final AE report is included in the attached table. A total of 464 adverse events (AEs) were recorded. One hundred twenty-four D-Met treated patients (78% or 124 out of 158) experienced a total of 294 AEs and 97 placebo patients (61% or 97 out of 160) experienced 170 AEs. None of these events were determined to be severe. All AEs resolved within 30 days. All AEs were classified as either mild or moderate and involved symptoms commonly associated with D-Met dosing (i.e. involved urine and/or body odor, nausea, vomiting, flatulence, diarrhea).
4. AE Dropouts: Drop-outs due to an AE were 18% (n = 18) and were typically associated with a complaint of GI disturbance. Of the drop-outs, n=15 out of the total reported were in the D-Met group. Although the drug demonstrated a positive safety profile from a clinical standpoint, subjects complained about palatability issues including unpleasant taste, smell and body odor. We suspect that these AEs could be reduced by a dry formulation dissolved in the intestine without the high sorbitol sweetener used in the current liquid formulation.
5. Bioanalytical. Final laboratory reports are included in the 7 attached PDF tables. There have been no clinically significant clinical lab findings suggestive of treatment related causality, albeit the data from the NIHL trial is very limited. Pregnancy testing and laboratory assessment for kidney function (GFR) were performed on all enrolled subjects at baseline. No subjects were withdrawn due to a positive pregnancy test or abnormal GFR. Additional safety assessments were added late in the trial (n = 37 subjects; 21 placebo / 16 active; sufficiently evaluable - 18 placebo / 13 active) to include: laboratory evaluations (hematology, blood chemistry, liver function, homocysteine and urinalysis) at pre-specified time points (e.g., pre-treatment, during treatment, and post-treatment). No clinically significant clinical lab changes were observed during or post-treatment, including any clinically significant homocysteine level change during or post-treatment. Bioanalytical results flagged as abnormal values were 100% verified to source documents.
6. Please note that further analyses will continue as we mine the database.

B: D-met Efficacy Including Percent Reduction in Hearing Threshold Shift

Outcome		All	Group		p-value (t-sided Fisher's Exact Test)	% Improvement in D- methionine Group Relative to Placebo
			D- methionin e	Place bo		
ASHA 1994 Criteria	Left Ear Shift	7.6	6.78	8.33	0.4133	18.6%
	Right Ear Shift	8.4	7.69	9.02	0.4422	14.7%
	Shift in Either Ear	14.69	13.91	15.38	0.4439	9.6%
	Shift in Both Ears	1.64	0.88	2.31	0.3619	61.9%

	Trigger Hand Ear Shift	7.6	6.84	8.27	0.4276	17.3%
	Non-trigger Hand Ear Shift	8.4	7.63	9.09	0.427	16.1%
DOEHRSHC Shift		1.56	1.67	1.47	0.7345	-13.6%
Early Warning Shift		5.86	4.17	7.35	0.2081	43.3%
Notes:						
1. Asha 1994 Criteria: A threshold shift is defined as:						
	: An increase of at least 20 dB at any one frequency,					
	: An increase of at least 10 dB at any two consecutive frequencies, or					
	: Loss of response at 3 consecutive frequencies where responses were obtained at baseline.					
2. DOEHRSHC Criteria: A threshold shift is defined as:						
	: Greater than or equal to 10 dB change for the average of 2k, 3k, and 4k in either ear.					
3. Early Warning Shift: A threshold shift is defined as:						
	: Greater than or equal to 15 dB change at 1k, 2k, 3k, OR 4k in either ear.					

C: Adverse Event (AE) Report

Summary of Safety

A total of 464 adverse events (AEs) were recorded (See Appendix. Table 2 Full List of AE Frequency and Table 3. List of AE including Study Arm). One hundred twenty-four D-Met treated patients (78% or 124 out of 158) experienced a total of 294 AEs and 97 placebo patients (61% or 97 out of 160) experienced 170 AEs. None of these events were determined to be severe. All AEs resolved within 30 days. All AEs were classified as either mild or moderate and involved symptoms commonly associated with D-Met dosing (i.e. involved urine and/or body odor, nausea, vomiting, flatulence, diarrhea).

Figure 1. Graph of AE Frequency

Reported Adverse Events (total 318 treated subjects)

